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# Is It Time to Switch the Focus of Murine Studies to Treatment Rather than Prevention in Abdominal Aortic Aneurysms?

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**Commentary**

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## Abstract

While there is a growing body of evidence to suggest possible mechanisms for Abdominal Aortic Aneurysm (AAAs) formation, few murine studies have identified successful translational targets for AAA therapy in patient settings. This commentary seeks to address the need for murine studies to focus on treatment of established AAAs in multiple models to have the best possible outcome for future patient intervention.

## Abbreviations

AA: Aortic Aneurysms; AAA: Abdominal Aortic Aneurysm; Ang II: Angiotensin II; BAPN: β-Aminopropionitrile; ECM: Extra-Cellular Matrix; TGFβ: Transforming Growth Factor Beta.

## Commentary

According to the Center for Disease Control's National Center for Injury Control, aortic aneurysms (AAs) were a leading cause of death in all races and both sexes from 1999-2016 and are described as a dilatation of a discrete portion of the vessel lumen by over 50% [1]. AAs can progress in silence, increasing in size until the structure of the aortic wall is so distorted that it eventually fails. Symptoms usually develop only when the aneurysm has reached a critical size (100-150% dilation) and is at high risk for dissection or rupture [2]. In one study, the 5-year mortality for untreated thoracic aortic aneurysm was 87%, with 74% of patients dying of rupture. Of those that ruptured, mortality was 94% [3]. In that same study the prevalence was 5.9 new aneurysms per 100,000 person-years, however with increased use of high resolution chest imaging, the true incidence appears to be much higher. A more recent study found the incidence of new aneurysm diagnoses to be 16.3 per 100,000 per year [4]. The actual burden of AA disease may still be an underestimate, as fatality due to AA complications are likely to be attributed to other pathologies, such as acute myocardial infarction, in patients who do not undergo a post-mortem autopsy [5]. As discussed earlier, as more patients undergo chest imaging for other diseases, an increasing number of asymptomatic, early aneurysms are discovered, and can be appropriately monitored, and if needed, repaired. In an elective setting, AA repair has 5 year survival of 85%, while emergency repair is much worse at 38% [6], underscoring the need for better understanding of the underlying cellular, mechanical, and hemodynamic processes involved in AA progression.

There has been decades of research toward examining the mechanisms that underlie and contribute to the development, progression and end stage clinical events including rupture [6]. Clinical management of patients with Abdominal Aortic Aneurysms (AAAs) is largely focused on monitoring the diameter of aortic dilation until it reaches a critical size followed by either open or endovascular corrective surgery [7]. Despite aggressive monitoring of patients with increasing aortic dilation and despite declines in aneurysm incidence in Europe due to declines in smoking, mortality rates from increasing aneurysm formation, dissections, and rupture remain very high [8-10]. As such, there is a need for more effective therapies to treat and prevent aneurysm formation. Despite numerous studies identifying multiple clinical risk factors for human AAA formation (i.e. male gender, smokers, COPD, hypertension, etc.), aortic aneurysms continue to be a significant public health issue [7].

Progress has been limited in developing targeted medical therapies to slow the growth and rupture of Abdominal aortic aneurysms (AAAs), implying there is a significant need to better understand aortic aneurysm pathogenesis if we are going to develop translatable therapies. Basic science research has identified multiple, primarily early targets (i.e. metalloproteinase [MMP], serine proteases, cathepsins, etc.) in AAA models that, when genetically deleted or pharmacologically targeted with inhibitors, serve to decrease growth rates and size in experimental models [8-14]. However, many of these targets also overlap with other inflammatory diseases and do not target the underlying pathology of aortic aneurysm disease. While inhibition of the TGFβ signaling pathway first appeared to carry great possibilities for the inhibition of AAAs, human trials provided mixed results in AAAs in humans [15-20]. While these studies and others demonstrated that the TGFβ signaling pathway plays a significant role in AAA formation, they did not attempt to examine the role of treatment of established aortic aneurysms similar to what is seen when human patients present clinically. Female gender has also been suggested to play a protective role in AAA formation [11,21-31]; however, the possible sexual side effects of estrogen therapies in males or inhibition of testosterone signaling in males would offset potential promising results. However, again many of these studies focus on prevention treatment studies rather than examine treatment of already established aneurysms similar to human disease. Targeting of cytokine pathways or extra-cellular matrix (ECM) inhibitors have also demonstrated mixed results clinically because many targets overlap with atherosclerosis or other types of vascular disease. Only recently have investigational studies begun to be performed in mice with small AAAs pharmacologically, similar to what would likely occur in human trials [32,33].

While our laboratory, like many other laboratories in the field, have published extensively using many of the described murine models such as the elastase perfusion and application models, and the Angiotensin II models [8-13,32,34], we have primarily used the elastase perfusion model followed with confirmation in the Angiotensin II model [34-39]. Our research, like most others, has primarily focused on inhibition of AAA formation by treating animals pharmacologically or altering specific genes before AAA induction and focused on early events in the aforementioned models. Clearly, this does not parallel how we would treat patients with aortic aneurysms, as our goal using directed pharmacologic or biologic therapy, would be to treat humans with small AAAs already present. Therefore, future studies investigating pharmacologic inhibition of AAAs should consider adding treatment of already established aneurysms in two models because treatment studies would represent advancements to the field of aneurysm research itself because we would focus on real-time events of chronic aneurysm formation and rupture and the translation of these events into a diagnostic tool for patients.

We also should consider including image tracking of aortic aneurysm size pre and post-treatment to be able to conclude whether AAAs possesses the ability to regress [40,41]. There are two lines of clinical evidence in humans that suggest that even large, end stage AAAs have the ability to regress or heal. First, in the United Kingdom Small Aortic Aneurysm trial comparing observation versus open surgical repair, approximately 5% of patients with infrarenal AAAs demonstrated regression of their aortic aneurysm over time [42-44]. The exact mechanisms behind this regression remain unknown. Second, and even more convincing that large AAAs can regress, is the observation that almost 75% of AAAs following endovascular AAA repair regress their diameter. In some AAAs, this regression is so remarkable that the aneurysm can go from well over 6 cm to the same diameter as the aortic grafts (roughly 2 cm). These two observations suggest that even end stage AAAs have the ability to heal and regress, thus making them less prone to rupture and death. These observations indicate there is some mechanism in the pathology of the disease that allows for regression. To date, this process has been poorly investigated and it should be our goal to investigate this process in much greater detail to determine what molecules could be responsible for this regression. However, part of this process will need to also include the development of novel ways to track aneurysm characteristics *in vivo* in real time, most likely using ultrasound microbubbles or PET-CT probes for example to label either the influx of certain inflammatory cytokines or certain phenotypic changes in smooth muscle cells recently characterized by multiple lineage tracing mouse models as defined in other cardiovascular diseases [45-48].

Often patients present with catastrophic aortic aneurysm rupture without actually knowing they even have an aneurysm. Recent national screening programs have attempted to address this as important public health issue by encouraging patients to screen for aneurysms after 65 years of age [49]. However, clearly a better understanding of the pathogenesis of AAA formation, as a chronic disease process, is important. Many murine models also fail to address the chronic, thrombotic aneurysm with continued growth and a possibility of rupture. For many years, this failing was addressed by using multiple murine models combined with genetic and pharmacologic inhibition to test hypotheses. Recently, to address the need for a chronic rupture model, several labs have begun targeting multiple pathways to produce rupture models. Lu et al., recently demonstrated a novel, chronic murine AAA model which results in ~50% aortic rupture over a 100 day duration [50]. This reproducible, chronic, clinically relevant murine model of AAA and aortic rupture demonstrated continued growth

using the lysyl oxidase inhibitor, β-aminopropionitrile (BAPN) in combination with the peri-adventitial elastase application model. Fashandi et al., also used BAPN but in combination with a high dose of Angiotensin II (Ang II) to induce rupture in ApoE knock-out mice [51]. Other groups have used Angiotensin II in combination with a neutralizing antibody to TGFβ to induce a chronic aneurysm with the possibility of rupture [52,53]. These new more chronic murine models will allow the field to begin to investigate the mechanisms of rupture in greater detail and will provide models to test for possible effects of regression of AAAs following treatment therapy.

Future studies will begin to require additional changes to our histological classification systems for defining the characteristics of more chronic and rupture-prone murine AAAs. Currently, we have few defining targets for aneurysm rupture that do not overlap with other cardiovascular diseases. Perhaps RNA-Seq technology of these murine models in the future will offer additional targets for use as possible PET-CT probes or as histological targets for rupture potential. Finally, developing a medical treatment therapy for AAAs will require additional studies into defining the mechanisms of AAAs versus descending thoracic aortic aneurysms. These two diseases share many characteristics and the same inflammatory cytokines; however, these diseases are in different aortic locations. While we can account for some region differences due to flow and the embryologic origin of the smooth muscle cells in each location [53], there are likely unknown mechanisms causing AAAs versus dTAAs that are independent of these factors. Again, perhaps RNA-Seq data will be able to offer some additional insights into possible associated or causal factors for the regional diversity of aneurysm disease characteristics. In conclusion, aneurysm research has found many diverse pathways and mechanisms explaining possible roles of various factors in the disease process; however, we are still searching for possible targeted therapies to halt disease progression and prevent rupture in human patients. The use of better murine models and pharmacologic treatment of small aneurysm in the newly developed chronic murine models will hopefully increase the possibility of finding regression treatment therapies.

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